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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/047,652	03/25/1998	VASSILIOS PAPADOPOULOS	009/064/SAP	3470

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/047,652	Papadopoulos et al
Examiner	**Art Unit**
MINH TAM DAVIS	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 20, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *53-68* is/are pending in the application.

4a) Of the above, claim(s) *58-63 and 66-68* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *53-57, 64, and 65* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 48-52 and adds new claims 53-68.

Since applicant has elected Group III, an antagonist of PBR, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of claims 58-62 directed to a method for inhibiting tumor cell proliferation, and the embodiments of claims 63, 66-68 directed to an antisense oligonucleotide which is comprised in a proteoliposome containing a viral envelope receptor proteins, or in a microbeads, or in a carrier, which is a cytokine or polylysine-glycoprotein, have been withdrawn from consideration as being directed to a non-elected invention and an antagonist of PBR will be examined. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03. Newly submitted claims 58-63, 66-68 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The method of claims 58-62 is distinct from the elected composition as product and process.

The compositions of claims 63, 66-68 are distinct from the elected composition, because the compositions of claims 63, 66-68 comprise additional compounds not found in the originally elected composition.

Accordingly, claims 53-57, 64-65 are being examined.

The following are the remaining rejections.

OBJECTION

Claim 53 is objected for the use of the grammatically incorrect language "are" having....

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 53-57, 64-65 are indefnite because it is not clear in claim 53 the antisense oligonucleotide or a portion of PBR has the nucleic acid sequence contained in SEQ ID NO:1 or SEQ ID NO:2.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT, NEW REJECTION

Claims 53-57, 64-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

New claims 53-57, 64-64 are drawn to an antisense oligonucleotide that has a structure complementary to a portion of the nucleic acid sequence contained in in SEQ ID NO:1 or 2, wherein said antisense oligonucleotide inhibits the expression of a cell line that expresses PBR gene, and thereby inhibits proliferation of said cell line. Said cell line could be a human breast cancer cell line.

The specification discloses that SEQ ID NO:1 and 2 are partial cDNA sequences of PBR identified in breast cancer cell lines MDA-231 and MCF-7, respectively (p.15), wherein the breast cancer cell line MDA-231 is more aggressive, and expresses PBR at higher level than the non-aggresive cell line MCF-7 (page 36 and table 1 on page 36). The specification further discloses that the region surrounding the translation site and 5' to the translation has not yet been obtained (p.16, lines 7-10). In other words, the size of the overexpressed PBR mRNA in MDA-231 and MCF-7 is not necessarily the same size as the isolated partial sequence corresponding to SEQ ID NO:1 or 2. The specification also discloses that by homologous recombination in rat Leydig tumor cell line, one allele of PBR gene is inactivated, resulting in suppression of mRNA expression of PBR and reduced cell growth (Example 7, on pages 45-46).

One cannot extrapolate the teaching in the specification to the claims, because Applicant does not teach how to use the instant antisense oligonucleotides in cell lines for diagnostic or screening purposes thus it is not clear what "practical use" could be made of cell lines produced with the instant method. Further, at the time of filing, and since, the design and employment of anti-sense nucleic sequences was a highly unpredictable art which required extensive

experimentation in the elaboration of appropriate nucleic acid constructs that, when introduced into a host cell, would effect an inhibition of expression of any particular gene or gene product. For example, the specification fails to teach whether any antisense oligonucleotides within the claimed partial cDNA sequence of SEQ ID NO:1 or 2, of all of the antisense oligonucleotides encompassed within the claims which would be expected to function as an effective antisense binding site. It was well known in the art at the time the invention was made that identification of such binding sites in a given mRNA species resulting in inhibition of gene expression is an unpredictable art. For instance, US Patent No. 5,585,479 (of record) discloses an effective oligonucleotide and show that moving the target just one or two bases, can greatly reduce of even eliminate, antisense activity (data disclosed in columns 15-17). US Patent No. 5,585,479 states that "there are no rational explanations or rules that would predict active sequences". Further, one cannot correlate the example on homologous recombination in rat Leydig tumor cell line, with the claims, because in said example, one whole allele of PBR gene is inactivated, and it is not predictable which sites on the whole length PBR sequence is responsible for inactivation of the expression of the PBR gene, and whether these sites would be contained in the partial cDNA sequences of SEQ ID No:1 or 2. Thus, in view of the unpredictability of whether antisense molecules within the claimed partial cDNA sequence of SEQ ID NO:1 or 2 would function effectively to inhibit PBR gene expression, and in the absence of evidence to the contrary, a skilled artisan would be unable to practice the claimed invention using the claimed antisense sequences without undue experimentation and with a reasonable expectation of success.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

New claim 65 is rejected under 35 USC pertaining to lack of enablement for *in vivo* use of the claimed antisense oligonucleotide, for the same reasons for the rejection of former claims 48-52, already of record in paper No.11, pages 4-5.

New claim 65 is drawn to an antisense oligonucleotide, that has a structure complementary to a portion of the nucleic acid sequence contained in in SEQ ID NO:1 or 2, wherein said antisense oligonucleotide is comprised in a vector which is expressed in the mammary gland.

New claim 65 encompass *in vivo* expression of an antisense oligonucleotide, that has a structure complementary to a portion of the nucleic acid sequence contained in in SEQ ID NO:1 or 2

Applicant argues that it is predictable that the sequences can be selected which will be effective, based on the information in the disclosure (Example 7) that inhibition of the expression of one allele of the PBR gene resulted in the reduction in cell proliferation of a cancer cell line. Applicant further argues that SEQ ID NO:1 and 2 which are partial cDNA sequences of PBR are identified in breast cancer cell lines MDA-231 and MCF-7, respectively (p.15), wherein the breast cancer cell line MDA-231 is aggressive. Applicant asserts that the expression of these sequences may represent an early event in the progression of the disease. Applicant further

asserts that nuclear PBR is responsible for regulating the movement of cholesterol into nuclear membrane, and that this regulation is related to the modulation of cell proliferation.

Applicant's arguments set forth in paper No.15 have been considered but are not deemed to be persuasive for the following reasons:

One cannot correlate the example on homologous recombination in rat Leydig tumor cell line, with the claims, because in said example, one whole allele of PBR gene is inactivated, and it is not predictable which sites on the whole length PBR sequence is responsible for inactivation of the expression of the PBR gene, and whether these sites would be contained in the partial cDNA sequences of SEQ ID No:1 or 2, *supra*. Further, even if an antisense oligonucleotide could be successfully used *in vitro* to inhibit the expression of a gene, it is unpredictable that said antisense oligonucleotide could be successfully used *in vivo*, because 1) successful application of antisense therapy *in vivo* has been extremely limited, and 2) even if the biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss (of record).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

November 21, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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